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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	13

DATE MAILED: 01/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/738,049	KAPLAN, DAVID R.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 10/24/02 in Paper No. 11 is acknowledged and has been entered. Claims 34-61 have been cancelled. Claims 1, 2, 5, 18, and 32 have been amended. Accordingly, claims 1-33 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 102/103

2. In light of Applicant's amendment, the rejection of claims 1-2, 5, 10, 14-18, 25-26, and 28-30 under 35 U.S.C. 102(b) as being anticipated by Karkmann et al. (Journal of Immunological Methods, 1999) is hereby, withdrawn.

3. In light of Applicant's amendment, the rejection of claims 1-2, 5, 11-19, and 23-33 under 35 U.S.C. 102(b) as being anticipated by Lollini et al. (Immunological Blackboard, 1998) is hereby, withdrawn.

4. In light of Applicant's amendment, the rejection of claims 3-4, 6-9, are 20-22 under 35 U.S.C. 103(a) as being unpatentable over Karkmann et al. (Journal of Immunological Methods, 1999) or Lollini et al. (Immunological Blackboard, 1998) is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "using isotype/subtype matched nonspecific immunoglobulin as a negative control" because it is unclear what is encompassed by the recitation of "isotype/subtype matched nonspecific immunoglobulin" and how it is used. It is further unclear what structural or functional cooperative relationship exists between the isotype/subtype matched nonspecific immunoglobulin and other elements in the claim, i.e. intracellular analyte, detectable label, so as to have utility as negative control for the claimed method.

Claim 2 is vague and indefinite in reciting, "using isotype/subtype matched nonspecific immunoglobulin as a negative control" because it is unclear what is encompassed by the recitation of "isotype/subtype matched nonspecific immunoglobulin" and how it is used. It is further unclear what structural or functional cooperative relationship exists between the isotype/subtype matched nonspecific immunoglobulin and other elements in the claim, i.e. intracellular analyte, detectable label, so as to have utility as negative control for the claimed method.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)* enablement requires that the specification teach those of skill in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of detecting the presence of intracellular analyte in cells by fixing the cells, permeabilizing the cells, catalyzing the deposition of tyramide in said cells, contacting detectable label that binds tyramide to the cells, then detecting a signal from the cells to indicate the presence of intracellular analyte in the cells by flow cytometry, wherein isotype/subtype matched nonspecific immunoglobulin is used as negative control.

The state of the prior art- the prior art of record fails to disclose a method of detecting the presence of intracellular analyte in cells by fixing the cells, permeabilizing

the cells, catalyzing the deposition of tyramide in said cells, contacting detectable label that binds tyramide to the cells, then detecting a signal from the cells to indicate the presence of intracellular analyte in the cells by flow cytometry, wherein isotype/subtype matched nonspecific immunoglobulin is used as negative control.

The predictability or lack thereof in the art- there is no predictability based on the instant specification how the isotype/subtype matched nonspecific immunoglobulin can be used as negative control in the claimed method.

The amount of direction or guidance present- the specification fails to provide adequate guidance to enable use of isotype/subtype matched nonspecific immunoglobulin as negative control in the claimed method.

The presence or absence of working examples- There are no working examples that exemplify use of isotype/subtype matched nonspecific immunoglobulin as negative control in accordance to the claimed method.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of detecting the presence of intracellular analyte in cells by fixing the cells, permeabilizing the cells, catalyzing the deposition of tyramide in said cells, contacting detectable label that binds tyramide to the cells, then detecting a signal from the cells to indicate the presence of intracellular analyte in the cells by flow cytometry, wherein isotype/subtype matched nonspecific immunoglobulin is used as negative control.

In this case, the mode of how the isotype/subtype matched nonspecific immunoglobulin is used as negative control in the claimed invention is not adequately described in the specification so as to be used in accordance with the claimed invention. Specifically, claims 1 and 2 recite:

a) fixing and permeabilizing (intracellular) cells.

b) catalyzing the deposition of tyramide in the cells,

c) contacting the cells with a detectable label that directly or indirectly binds to tyramide; whereby the cells comprising the intracellular analyte are specifically labeled, and, (*tyramide may alternatively be conjugated to the detectable label- for claim 2*)

d) detecting a signal from said cells comprising the detectable label using a flow cytometric device, ...wherein said signal is at least 10-fold greater that a signal obtainable by standard flow cytometry using isotype/subtype matched nonspecific immunoglobulin as a negative control.

However, the specification only provides a general comment at page 9, line 30 to page 10, line 5 that proper isotype/subtype matched antibodies must be used in order to obtain proper control measurements. According to Applicant, low nonspecific background levels and enhanced peak signal separation between histograms obtained from *cells stained with control immunoglobulin* versus *cells stained with immunoglobulin specific for the analyte of interest* can be advantageously provided in comparison to traditional staining method (page 19, first full paragraph and page 23, second full paragraph). In conventional or standard laboratory practice, a positive control

comprises cells having a specific intracellular antigen and are stained using an antigen specific antibody conjugated to a detectable label, i.e. fluorescein, a negative control comprises cells not expressing the antigen, or cells having the intracellular antigen but are stained using an antigen specific antibody in the absence of a the fluorescein; and all of the positive control, negative control, and patient sample suspected of having the intracellular antigen are treated in the same manner, in this case, as recited in the method steps of the claimed invention by Applicant, save for the lack of fluorescein conjugated to the antigen specific antibody for the negative control having cells expressing the intracellular antigen. See for example Karkmann et al. and Lollini. However, as set forth in Applicant's disclosure, the use of "isotype/subtype matched nonspecific immunoglobulin or antibodies as negative control" in the specification appears to encompass more of its use in a staining method and composition that deviates from the elements delimiting the recited claims. In lines 24-33 at page 24, Applicant further shows that an increased amount of serum to between 25% to 100% of serum or serum albumin with or without detergent treatment, reduces nonspecific background staining dramatically, with a resulting increase in peak signal separation between *specific and control antibodies* in the flow cytometer; likewise a teaching incongruent with the elements, i.e. fixative, permeabilizer, tyramide, conjugated antibody that binds tyramide, of the claimed invention.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed

method to use isotype/subtype matched nonspecific immunoglobulin or antibodies as negative control in accordance to the claimed invention, would be great as 2) there is no experimental evidence provided that would indicate how the isotype/subtype matched nonspecific immunoglobulin works in accordance to the claimed method as a negative control; 3) there is no proper guidance that shows using isotype/subtype matched nonspecific immunoglobulin as a negative control in accordance to the claimed invention, guidance suggests its use as a deviated staining composition and method distinct from that taught in the claimed invention, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows using isotype/subtype matched nonspecific immunoglobulin as a negative control with the claimed method, and lastly 7) the claims broadly recite a method of detecting the presence of intracellular analyte in cells by fixing the cells, permeabilizing the cells, catalyzing the deposition of tyramide in said cells, contacting detectable label that binds tyramide to the cells, then detecting a signal from the cells to indicate the presence of intracellular analyte in the cells by flow cytometry, wherein isotype/subtype matched nonspecific immunoglobulin is used as negative control, without specifically stating how it is done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Response to Arguments and Applicant's Declaration

7. Applicant's arguments with respect to claims 1-33 have been considered but are moot in view of the new grounds of rejection.

A) Applicant contends that the instant claims distinguish over the Karkmann et al. and Lollini publications because these cited publications do not disclose using isotype/subtype matched nonspecific immunoglobulin as a negative control, as required by the amended claims.

Applicant's contention is in accordance to Karkmann's and Lollini's teaching. Accordingly, the rejections of the claims as being anticipated by Karkmann and Lollini have been withdrawn.

B) Applicant contends that antibodies adhere to certain types of cells in a manner than is not dependent on the antigenic specificity of the antibody; therefore, it is important to verify the specificity of binding. Applicant states that verification of specificity can be ascertained by use of nonspecific isotype/subtype matched immunoglobulin controls.

In response, Applicant's contention is confusing because as the name implies, the isotype or subtype matched immunoglobulin controls are nonspecific. Accordingly, it is unclear how the nonspecific isotype or subtype matched immunoglobulin controls verify the specificity of binding in the claimed method. Furthermore, a review of Applicant's disclosure provides no evidentiary showing how the nonspecific isotype or

subtype matched immunoglobulin is used as a negative control in accordance to the recited or claimed method.

8. For reasons aforementioned, no claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday, 6:30-1630, and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
January 16, 2003

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641
1/10/03